Acute Pancreatitis in Japan

Comparison of Before and After Revision of the Clinical Guidelines

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Objectives: Cases of acute pancreatitis (AP) are increasing worldwide, and mortality remains high in severe cases. In 2015, the Japanese guidelines for the management of AP were revised. We aimed to clarify the clinical practice of AP in Japan and its trend during the revision of the guidelines using a Japanese nationwide administrative database.

Methods: We retrospectively analyzed 102,119 patients with AP who were hospitalized between April 2014 and March 2018. The study period was divided into the first period (the time before the revision: fiscal years 2014 and 2015) and second period (after the revision: 2016 and 2017).

Results: Severe cases of AP accounted for 27.7% of total cases. The in-hospital mortality in severe cases was 5.7%. The mortality within 14 days of admission improved from 3.2% in the first period to 2.6% in the second period ($P = 0.022$). Referred patients had more severe diseases and a higher mortality. The mortality in patients who underwent endoscopic ultrasound-guided fistuloplasty for local complications (11.6%) was lower than that in patients who underwent percutaneous drainage (23.4%) or AP surgery (22.6%) ($P < 0.001$).

Conclusions: We clarified the clinical practice of AP including the improved mortality after the revision of the guidelines.

Key Words: DPC, endoscopic necrosectomy, endoscopic ultrasound-guided transluminal drainage, pancreatitis bundles, walled-off necrosis

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Acute pancreatitis (AP) is an acute inflammatory disorder of the pancreas,[1–3] and the number of cases of AP is increasing worldwide.[4–6] Most patients with AP have mild illness; however, approximately 20% of patients with AP develop severe diseases, complicated with pancreatic necrosis and multiple organ failure, which may eventually be fatal, with a mortality as high as 30%.[1–3,7] Up-to-date information on the actual clinical management of AP is essential for the validation and revision of guidelines. The Japanese guidelines for the management of AP were revised in 2015[8]; however, the impact of the revision on the clinical management of AP remains unclear. To clarify the current status of AP, nationwide epidemiological surveys of AP have been conducted every 4 to 5 years in Japan.[6,9] The estimated number of cases of AP has continuously increased over the last 3 decades, reaching 78,450 in 2016, which is 25% higher than that in 2011.[9] Of note, the mortality in patients with severe AP dramatically decreased by 40%, from 10.1% in 2011 to 6.1% in 2016. Although nationwide surveys have provided invaluable information about the clinical practice of AP in Japan, they might have potential biases because they were responder-based surveys.[6,9] Therefore, the findings of these surveys need to be validated using unbiased samples.

The Japanese diagnosis procedure combination (DPC) is a patient classification system that includes discharge abstracts and administrative claims data.[10,11] The Japanese DPC is linked to a payment system for inpatients and covers approximately 50% of a nonstratified sample of Japanese hospitals including more than 1200 acute care hospitals and all academic hospitals. The DPC database registers data on the main diagnosis coding based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) for each hospitalization. The database includes basic hospitalization information such as age, sex, comorbidities at admission, dates of admission and discharge, history of admission to the intensive care unit (ICU), medications and interventional procedures, and outcomes at discharge. Using the DPC database, previous studies have revealed the clinical practice of AP in Japan.[12–14] This study aimed to clarify the updated clinical practice of AP in Japan as well as its trend before and after the revision of the Japanese guidelines using the DPC database.

MATERIALS AND METHODS

Data Collection

Using the DPC database, we identified patients with a principal diagnosis of AP (*ICD-10* code K85) and patients in whom the diagnosis of AP accounted for most of the medical expenses who were hospitalized between April 1, 2012, and March 31, 2018. We divided the study period into the first period, which included the time before the revision, that is, fiscal years 2014 and 2015, and second period, which included the time after the revision, that is, fiscal years 2016 and 2017.

The Charlson comorbidity index (CCI) was used for categorizing comorbidities in patients based on the *ICD* diagnosis codes.[15] Protease inhibitors (PIs) included nafamostat mesylate, gabexate mesylate, and ulinastatin. Antibiotics included carbapenems; second-,

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M.I., S.H., K.T., and A.M. designed the study. K.T., K. Fujimori, and K. Fushimi retrieved the data from the diagnosis procedure combination database. M.I., S.H., K.K., T.T., N.Y., R.M., Y.T., F.K., A.S. K.T., K. Fujimori, and A.M. analyzed the data. M.I. and A.M. drafted the manuscript, and A.M. edited the manuscript. All authors read and approved the final manuscript.

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TABLE 1. Characteristics of the AP Patients According to the Study Period

	All Periods (n = 102,219)	First Period 2014 and 2015 (n = 49,637)	Second Period 2016 and 2017 (n = 52,482)	*P**
Sex, male, n (%)	66,508 (65.1)	32,433 (65.3)	34,075 (64.9)	0.17
Age at AP onset, mean (SD), y				
All	61.4 (18.9)	61.1 (18.8)	61.7 (18.9)	<0.001
Male	59.0 (17.5)	58.7 (17.4)	59.3 (17.6)	<0.001
Female	65.9 (20.5)	65.6 (20.5)	66.1 (20.5)	0.022
CCI, n (%)				<0.001
0	43,810 (42.9)	21,399 (43.1)	22,411 (42.7)	
1–2	42,772 (41.9)	21,142 (42.6)	21,630 (41.2)	
>3	15,537 (15.2)	7096 (14.3)	8441 (16.1)	
Severity,† n (%)				<0.001
Mild AP	57,485 (72.3)	28,696 (73.5)	28,789 (71.2)	
Severe AP	21,970 (27.7)	10,347 (26.5)	11,623 (28.8)	
Admission to ICU, n (%)	6179 (6.1)	3024 (6.1)	3155 (6.0)	0.59
Hospital type, academic, n (%)	10,698 (10.5)	5086 (10.3)	5612 (10.7)	0.020
Cases transferred from other institutions, n (%)	4850 (4.7)	2351 (4.7)	2499 (4.8)	0.85
LOS, mean (SD), d	18.0 (26.3)	18.5 (30.3)	17.6 (21.9)	<0.001

*Comparison between the first and second periods.

†Cases whose severity could be determined according to the Japanese severity criteria.

third-, and fourth-generation cephems; piperacillin; and β-lactamase inhibitor combination such as sulbactam/ampicillin and tazobactam/piperacillin. Antifungal agents included fluconazole, fosfluconazole, itraconazole, voriconazole, micafungin, caspofungin, and amphotericin B. We identified patients who received enteral nutrition (EN) as those who were registered in the database under the practice code of 140054710 for tube feeding with elemental diet. We identified patients who underwent therapeutic interventions as those who were registered in the database under the practice code of 150362410 for undergoing endoscopic ultrasound (EUS)–guided fistuloplasty, 150347510 for undergoing percutaneous abscess drainage, and 150348210 for undergoing AP surgery.

This study was performed in accordance with the principles of the Declaration of Helsinki. This study was approved, and the requirement for written informed consent was waived because of the anonymous nature of the data by the Ethics Committee of Tohoku University Graduate School of Medicine (approval no. 2021-1-029).

Statistical Analysis

Continuous variables are presented as mean (standard deviation [SD]), and they were compared using analysis of variance and Welch *t* test. We used Pearson χ^2 test to compare the proportions of 2 populations that have a specific characteristic. Statistical analyses were performed using JMP 15 (SAS Institute Inc, Cary, NC). Statistical significance was set at $P < 0.05$.

RESULTS

Patient Characteristics

During the study period, we identified a total of 102,119 patients (66,508 males and 35,611 females) with AP, including 49,637 patients in the first period (fiscal years: 2014 and 2015) and 52,482 patients in the second period (fiscal years: 2016 and 2017) (Table 1). In this study, the male-to-female ratio was 1.87:1. The mean age of all patients was 61.4 (SD, 18.9) years (59.0 [SD, 17.5] years in males and 65.9 [SD, 20.5] years in females) (Fig. 1). The most affected age range was 60 to 69 years in males and 80 to 89 years in females. On average, female patients were older than male patients ($P < 0.001$). Furthermore, the mean age at onset of AP in the second period was higher than that in the first period (61.7 vs 61.1 years, $P < 0.001$). The CCI was 0 in 43,810 cases (42.9%), 1 to 2 in 42,772 cases (41.9%), and 3 or greater in 15,537 cases (15.2%). The proportion of patients with CCI of 3 or greater was greater in the second period than that in the first period ($P < 0.001$). A total of 10,698 patients (10.5%) with AP were treated at an academic hospital. Approximately 5% of patients were referred from other institutions, and 6.1% of patients required ICU admission. The mean length of hospital stay (LOS) in the second period was shorter than that in the first period (17.6 vs 18.5 days, $P < 0.001$).

Severity

The severity of AP was determined at admission according to the Japanese severity criteria (see Supplemental Table 1, http://links.lww.com/MPA/A931, which indicates the Japanese severity criteria) in 79,455 patients (77.7%)[16]; among them, 57,485 (72.3%, 37,837 males and 19,648 females) were classified as patients with mild AP, and 21,970 (27.7%, 14,474 males and 7496 females) were

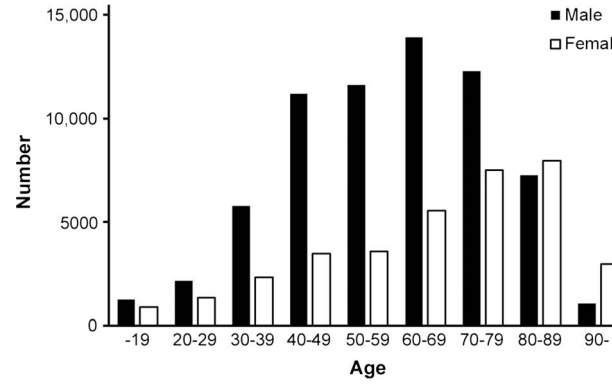

FIGURE 1. Age distribution of AP patients according to sex.

classified as patients with severe AP (Table 2). The number of severe cases was 10,347 in the first period and 11,623 in the second period. The age of patients with severe AP was 61.7 (SD, 18.9) years (58.6 [SD, 17.6] years in males and 67.7 [SD, 19.9] years in females) (see Supplemental Fig. 1, http://links.lww.com/MPA/A931, which indicates age distribution of severe AP patients). The most affected age range was 60 to 69 years in males and 80 to 89 years in female patients. The age at disease onset was higher in patients with severe AP than that in patients with mild AP ($P < 0.001$). The proportion of patients who required ICU admission and underwent treatment at academic hospitals was higher in patients with severe AP than that in patients with mild AP; moreover, the LOS in patients with severe AP was longer than that in patients with mild AP (Table 2).

Of the 21,970 patients with severe AP, 15,263 patients (69.5%) were classified as severe according to the computed tomography (CT) grading only, 2775 patients (12.6%) according to the prognostic factors only, and 3932 patients (17.9%) according to both CT grading and prognostic factors. In patients fulfilling CT grading only, the CT grade was 2 in 12,394 (81.2%), 3 in 1996 (13.1%), and 4 in 873 (5.7%). Among patients who fulfilled both prognostic factors and CT grading, the CT grade was 2 in 2441 (62.1%), 3 in 1102 (28.0%), and 4 in 389 (9.9%). The proportion of patients presenting with CT grade 2 was higher in those fulfilling CT grading only than in those fulfilling both the prognostic factors and CT grading ($P < 0.001$) classifications. Patients who were diagnosed with severe AP based on both prognostic factors and CT grading had the longest LOS (36.7 [SD, 45.9] days), followed by patients who were diagnosed with severe AP based on prognostic factors only (27.9 [SD, 33.9] days) and patients who were diagnosed with severe AP based on CT grading only (21.1 [SD, 22.5] days). The LOS was longer in patients who were treated in academic hospitals than that of patients who were treated in nonacademic hospitals (21.2 [SD, 26.7] days vs 17.7 [SD, 26.2] days, $P < 0.001$).

In-Hospital Mortality

We assessed in-hospital mortality, which included both AP-related mortality and mortality unrelated to AP. The overall in-hospital mortality was 2.9% (2933/102,119). Mortality increased with age, and because female patients with AP were older than male patients, the mortality in female patients was higher than that of male patients (1220/35,611 [3.4%] vs 1713/66,508 [2.6%], $P < 0.001$). However, if stratified by age groups, the mortality in male patients was higher than that in female patients in almost all age groups, except for those aged 40 to 49 years (Fig. 2). In the case of severe AP, the overall mortality was 5.7%: 6.0% in the first period and 5.4% in the second period ($P = 0.082$) (Table 3). According to the Japanese criteria for severity, mortality was 11.1% in patients who were diagnosed with severe AP based on prognostic factors only, 2.3% in patients who were diagnosed with severe AP based on CT grading only, and 15.0% in patients who were diagnosed with severe AP based on both prognostic factors and CT grading (see Supplemental Table 2, http://links.lww.com/MPA/A931, which indicates the mortality according to the Japanese severity criteria). In patients who were diagnosed with severe AP based on CT grading only, the mortality increased with increasing CT grading; the mortality was 1.9%, 3.6%, and 5.7% in patients with CT grading 2, 3, and 4, respectively ($P < 0.001$).

In patients with severe AP, the mortality within 14 days of admission (early mortality) decreased from 3.2% in the first period

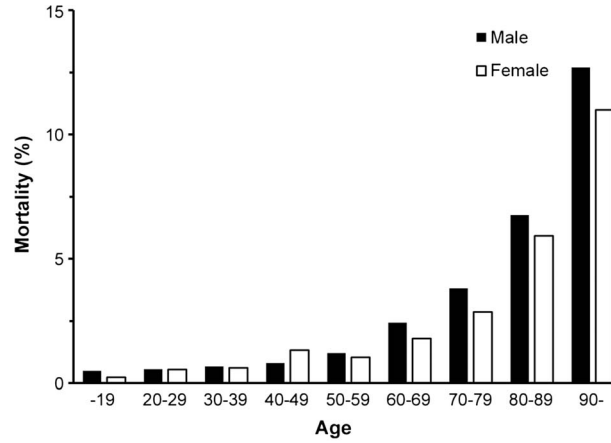

FIGURE 2. Mortality of AP patients according to age and sex.

TABLE 2. Characteristics of the AP Patients According to Severity

	All AP (n = 102,119)	Mild AP (n = 57,485)	Severe AP (n = 21,970)	P*
Sex, male, n (%)	66,508 (65.1)	37,837 (65.8)	14,474 (65.9)	0.87
Age at onset, mean (SD), y				
All	61.4 (18.9)	60.6 (18.5)	61.7 (18.9)	<0.001
Male	59.0 (17.5)	58.4 (17.2)	58.6 (17.6)	0.21
Female	65.9 (20.5)	64.7 (20.2)	67.7 (19.9)	<0.001
CCI, n (%)				<0.001
0	43,810 (42.9)	25,576 (44.5)	9357 (42.6)	
1–2	42,772 (41.9)	23,772 (41.4)	9603 (43.7)	
>3	15,537 (15.2)	8137 (14.1)	3010 (13.7)	
Admission to ICU, n (%)	6179 (6.1)	1818 (3.2)	3034 (13.8)	<0.001
Hospital type, academic, n (%)	10,698 (10.5)	5105 (8.9)	2723 (12.4)	<0.001
Cases transferred from other institutions, n (%)	4850 (4.7)	1730 (3.0)	1939 (8.8)	<0.001
Mortality, n (%)	2933 (2.9)	573 (1.0)	1251 (5.7)	<0.001
LOS, mean (SD), y	18.0 (26.3)	14.8 (14.0)	24.8 (30.1)	<0.001
Intervention,† n (%)	1307 (1.3)	344 (0.6)	648 (3.0)	<0.001

*Comparison between mild and severe AP cases.

†Intervention for local complications.

TABLE 3. Mortality According to the Study Periods and Time From Admission

	All Periods	First Period 2014 and 2015	Second Period 2016 and 2017	P*
All AP,† no. fatal cases (%)	2933 (2.9)	1427 (2.9)	1506 (2.9)	0.96
Within 14 d	1316 (1.3)	640 (1.3)	676 (1.3)	0.99
After 15 d	1617 (1.6)	787 (1.6)	830 (1.6)	0.96
Mild AP,‡ no. fatal cases (%)	573 (1.0)	278 (1.0)	295 (1.0)	0.50
Within 14 d	211 (0.4)	96 (0.3)	115 (0.4)	0.20
After 15 d	362 (0.6)	182 (0.6)	180 (0.6)	0.89
Severe AP,§ no. fatal cases (%)	1251 (5.7)	619 (6.0)	632 (5.4)	0.082
Within 14 d	634 (2.9)	327 (3.2)	307 (2.6)	0.022
After 15 d	617 (2.8)	292 (2.8)	325 (2.8)	0.91

*Comparison between the first and second period.

†The number of AP patients was 102,119 in the entire period: 49,637 in the first period and 52,482 in the second period.

‡The number of mild AP patients was 57,485 in the entire period: 28,696 in the first period and 28,789 in the second period.

§The number of severe AP patients was 21,970 in the entire period: 10,347 in the first period and 11,623 in the second period.

to 2.6% in the second period ($P = 0.022$). However, the mortality after 14 days of admission (late mortality) remained unchanged (2.8% in both the periods). These results suggest that improved management of AP within 14 days of admission contributed to improvement in mortality in patients with severe AP, and the management of AP thereafter remains a challenge.

Comparison Between Patients According to the Route of Admission

According to the Japanese guidelines for the management of AP,[8] patients with severe AP should immediately be referred to higher-level facilities if sufficient treatment for severe AP cannot be provided. We compared patients who were directly admitted with those who were referred from other institutions. Of 102,119 patients with AP, 97,269 (95.3%) were directly admitted, and 4850 (4.7%) were referred from other institutions (Table 4). Severe AP accounted for 52.9% of the cases whose severity could be determined. Compared with directly admitted patients, referred patients had a higher proportion of males, higher age at onset, and higher CCI. Compared with directly admitted patients, referred patients were more frequently treated at academic hospitals, required ICU admissions more frequently, and had longer LOS. The mortality in referred patients with severe AP was higher than that in directly admitted patients (10.5% [203/1939] vs 5.2% [1048/20,031], $P < 0.001$).

Management

Initial Fluid Resuscitation

We examined the total volume of fluid resuscitation during the first 3 days of admission. The mean volume was 6323 (SD, 6665) mL in all patients with AP, 6050 (SD, 5045) mL in patients with mild AP, and 7716 (SD, 4535) mL in patients with severe AP (see Supplemental Table 3, http://links.lww.com/MPA/A931, which indicates the fluid volume during the first 3 days of admission). The volume in severe cases of AP was greater than that in mild cases of AP ($P < 0.001$). When stratified by the study period, the total volume of fluid resuscitation during the first 3 days of admission was lower in the second period than that in the first period, regardless of the severity of AP.

Protease Inhibitors

Protease inhibitors were given to a total of 85,225 patients (83.5%) with AP. Among them, 47,743 patients (83.1%) had mild

TABLE 4. Characteristics of AP Patients According to Admission Route

	All AP (n = 102,119)	Direct (n = 97,269)	Transfer (n = 4850)	P*
Sex, male, n (%)	66,508 (65.1)	63,540 (65.3)	2968 (61.2)	<0.001
Age at onset, mean (SD), y	61.4 (18.9)	61.3 (18.8)	63.6 (19.7)	<0.001
CCI, n (%)				0.0026
0	43,810 (42.9)	41,817 (43.0)	1993 (41.1)	
1–2	42,772 (41.9)	40,625 (41.8)	2147 (44.3)	
>3	15,537 (15.2)	14,827 (15.2)	710 (14.6)	
Severe AP, n (%)†	21,970/79,455 (27.7)	20,031/75,786 (26.4)	1939/3669 (52.8)	<0.001
Admission to ICU, n (%)	6179 (6.1)	5540 (5.7)	639 (13.2)	<0.001
Hospital type, academic, n (%)	10,698 (10.5)	9329 (9.6)	1369 (28.2)	<0.001
Mortality, n (%)	2933 (2.9)	2558 (2.6)	375 (7.7)	<0.001
LOS, mean (SD), y	18.0 (26.3)	17.5 (25.6)	28.3 (36.4)	<0.001

*Comparison between the directly admitted cases and transferred cases.

†Cases whose severity could be determined according to the Japanese severity criteria.

AP, and 19,590 patients (89.2%) had severe AP (Table 5). Protease inhibitors were more frequently administered to patients with severe AP than that to patients with mild AP (89.2% vs 83.1%, $P < 0.001$). The proportion of patients who received PIs was lower in the second period than that in the first period, regardless of the severity of AP ($P < 0.001$).

Antibiotics

Antimicrobial drugs were administered to a total of 79,986 patients (78.3%) with AP, including 42,752 patients (74.4%) with mild AP. Carbapenems were used in 12,612 patients (21.9%) with mild AP. On the other hand, antimicrobial drugs were administered to 19,845 patients (90.3%) with severe AP. The proportion of patients with mild AP who received antimicrobial drugs was lower in the second period than that in the first period (77.3% vs 79.4%, $P < 0.001$).

Antifungal drugs were administered to 970 patients with AP. Antifungal drugs were more frequently administered to patients with severe AP than to patients with mild AP (2.2% vs 0.3%, $P < 0.001$).

Enteral Nutrition

Enteral nutrition was performed in a total of 4756 patients (4.7%) with AP, including 2234 patients (4.5%) in the first period and 2522 patients (4.8%) in the second period. To manage severe AP, EN was performed in 1345 patients (13.0%) in the first period and 1509 patients (13.0%) in the second period. Enteral nutrition was started in 1070 patients (4.9%) within 3 days of admission, in 861 patients (3.9%) within 4 to 7 days of admission, in 522 patients (2.4%) within 8 to 14 days of admission, and in 401 patients (1.8%) after 14 days of admission.

Interventions for Local Complications

Interventions for local complications were performed in a total of 1307 patients, including 579 patients in the first period and 728 patients in the second period. Initial interventions for local complications included EUS-guided fistuloplasty performed in 666 cases, percutaneous drainage performed in 482 cases, and AP surgery performed in 159 cases (including overlapping cases). The proportion of patients who underwent EUS-guided fistuloplasty as an initial treatment for local complications increased from 45.1% in the first period to 55.6% in the second period ($P < 0.001$) (Table 6). However, the proportion of patients who underwent AP surgery decreased from 15.2% in the first period to 9.8% in the second period ($P = 0.003$) (Table 6). The proportion of patients who underwent percutaneous drainage as an initial treatment for local complications tended to decrease from 39.7% in the first period to 34.6% in the second period; however, this change was not statistically significant ($P = 0.057$). The mortality in patients who underwent EUS-guided fistuloplasty as an initial treatment for local complications (11.6%) was lower than that of patients who underwent percutaneous drainage (23.4%) or AP surgery (22.6%) ($P < 0.001$). On the other hand, the mortality in patients who underwent EUS-guided fistuloplasty only was lower than that of patients who underwent other interventions in addition to EUS-guided fistuloplasty (9.4% [56/595] vs 29.8% [28/94], $P < 0.001$) (Table 7).

DISCUSSION

In this study, we revealed the clinical practice of AP in Japan using the DPC database, which is a large population-based database. Because the majority of the patients with AP are admitted to acute care hospitals, the DPC database, which mainly consists

TABLE 5. Treatment According to the Study Period

	All Periods (n = 102,119)	First Period 2014 and 2015 (n = 49,637)	Second Period 2016 and 2017 (n = 52,482)	P*
PIs, n (%)				
All AP	85,225 (83.5)	42,416 (85.5)	42,809 (81.6)	<0.001
Mild AP†	47,743 (83.1)	24,451 (85.2)	23,292 (80.9)	<0.001
Severe AP‡	19,590 (89.2)	9398 (90.8)	10,192 (87.7)	<0.001
Antimicrobial drugs, n (%)				
All AP	79,986 (78.3)	39,427 (79.4)	40,559 (77.3)	<0.001
Mild AP†	42,752 (74.4)	21,739 (75.8)	21,013 (73.0)	<0.001
Severe AP‡	19,845 (90.3)	9453 (91.4)	10,392 (89.4)	<0.001
Carbapenems, n (%)				
All AP	31,106 (30.5)	15,674 (31.6)	15,432 (29.4)	<0.001
Mild AP†	12,612 (21.9)	6635 (23.1)	5977 (20.8)	<0.001
Severe AP‡	12,579 (57.3)	6119 (59.1)	6460 (55.6)	<0.001
Antifungal drugs, n (%)				
All AP	970 (0.9)	490 (1.0)	480 (0.9)	0.23
Mild AP†	165 (0.3)	75 (0.3)	90 (0.3)	0.25
Severe AP‡	486 (2.2)	241 (2.3)	245 (2.1)	0.27
EN, n (%)				
All AP	4756 (4.7)	2234 (4.5)	2522 (4.8)	0.021
Mild AP†	927 (1.6)	427 (1.5)	500 (1.7)	0.018
Severe AP‡	2854 (13.0)	1345 (13.0)	1509 (13.0)	0.97

*Comparison between the first and second periods.

†The number of mild AP patients was 57,485 in the entire period, 28,696 in the first period, and 28,789 in the second period.

‡The number of severe AP patients was 21,970 in the entire period, 10,347 in the first period, and 11,623 in the second period.

TABLE 6. Initial Interventions for the Treatment of Local Complications According to the Study Period

	All Periods (n = 1307)	First Period 2014 and 2015 (n = 579)	Second Period 2016 and 2017 (n = 728)	*P**
EUS-guided fistuloplasty, n (%)	666 (51.0)	261 (45.1)	405 (55.6)	0.001
Percutaneous drainage, n (%)	482 (36.9)	230 (39.7)	252 (34.6)	0.057
Surgery, n (%)	159 (12.2)	88 (15.2)	71 (9.8)	0.003

*Comparison between the first and second periods.

of the data from acute care hospitals,[10,11] is useful for clarification of the clinical management of AP in an unbiased manner. We obtained data of more than 100,000 patients with AP or 25,000 patients with AP annually from the DPC database, which accounted for more than 30% of the estimated annual number of patients with AP (78,500 in 2016).[6] The latest Japanese nationwide epidemiological survey targeting patients with AP who were treated in 2016 reported a male-to-female sex ratio of 2.0 and a mean age at onset of 59.9 years in males and 66.5 years in females.[6] Of all cases of AP, 23.6% were classified as severe, and the AP-associated mortality in severe cases of AP was 6.1%. The age at disease onset in female patients was higher than that in male patients probably because of the differences in the etiology of the disease between men and women; the most common cause of AP was alcohol in males and gallstones in females.[1–3] Overall, the characteristics of patients with AP in this study were similar to those reported in the latest nationwide survey,[6] validating the nationwide epidemiological survey and the utility of the DPC database in clarifying the current status of AP in Japan.

To the best of our knowledge, this is the first study to reveal the current status of referred patients with AP across Japan. Our study showed that referred patients with AP had more severe diseases that required management at academic hospitals, ICU admissions, interventions for local complications, and longer LOS and had a higher mortality than directly admitted patients. These results agree with those of previous reports from the United States.[17,18] Kamal et al[17] reported an association between referral status and in-hospital mortality in patients with AP. Recently, Badal et al[18] reported the status of interhospital transfers and its impact on hospital outcomes in patients with AP. Multivariable analysis showed that old age, men, low-income quartiles, admission to a nonacademic hospital, gallstone pancreatitis, pancreatic surgery, and severe AP were predictors of referral from small or medium-sized hospitals. The analysis also showed that patients who had been referred to a larger tertiary care hospital had more severe diseases; underwent more endoscopic retrograde cholangiopancreatography sessions, more biliary decompression procedures, and pancreatic surgical procedures; and had a higher mortality than those who had not been referred. Although our study focused only on patients who were referred to higher-level centers, our results generally agreed with those reported by Badal et al.[18] It is reasonable to assume that the high mortality in referred patients resulted from the severe nature of their disease and not from the referral itself. Standardization of referral protocols and timeliness of intensive care are required to improve the mortality in referred patients.

We here compared the outcome in patients who were admitted before (first period: 2014 and 2015) and after the revision (second period: 2016 and 2017) of the Japanese guidelines for the management of AP in 2015. Mortality tended to improve in the second period despite the increase in the age at onset and proportion of patients with a CCI of 3 or greater. Clinical indicators, which are referred to as "pancreatitis bundles" (PBs) in the Japanese guidelines, consist of a bundle of 10 statements mainly specifying the management and treatment in the very early phase of hospitalization.[8] Implementation of PB was associated with reduced mortality in patients with severe AP.[19] The mortality was lower in patients who were treated with the implementation of 8 or more PB items than that in patients who were treated without the implementation of 8 or more PB items (1.0% vs 7.1%, $P = 0.02$). These results suggest that compliance with the guidelines, as shown by the implementation of PB, contributed to the improved mortality in the early phase of hospitalization after revision of the guidelines. On the

TABLE 7. Characteristics of the Patients According to the Treatments for Local Complications

	E Only (n = 595)	E + P (n = 55)	E + S (n = 30)	E + P + S (n = 9)	*P**
Sex, males, n (%)	445 (74.8)	30 (54.6)	22 (73.3)	5 (55.6)	0.008
Age at AP onset, mean (SD), y	62.7 (14.3)	61.7 (14.8)	61.5 (11.3)	67.6 (10.7)	0.68
CCI, n (%)					0.95
0	188 (31.6)	14 (25.5)	11 (36.7)	3 (33.3)	
1–2	273 (45.9)	28 (50.9)	14 (46.7)	4 (44.4)	
>3	134 (22.5)	13 (23.6)	5 (16.6)	2 (22.2)	
Severe cases, n (%)†	262/458 (57.2)	40/44 (90.9)	21/23 (91.3)	7/7 (100)	<0.001
Admission to ICU, n (%)	126 (21.2)	25 (45.5)	18 (60.0)	3 (33.3)	<0.001
Hospital type, academic, n (%)	231 (38.8)	22 (40.0)	12 (40.0)	4 (44.4)	0.98
Transferred cases, n (%)	147 (24.7)	19 (34.6)	7 (23.3)	4 (44.4)	0.23
Mortality, n (%)	56 (9.4)	16 (29.1)	7 (23.3)	5 (55.6)	<0.001
LOS, mean (SD), d	55.4 (44.1)	135.1 (86.4)	120.3 (55.0)	263.2 (362.5)	<0.001

*Comparison between four groups.

†Cases whose severity could be determined according to the Japanese severity criteria.

E indicates EUS-guided fistuloplasty; P, percutaneous drainage; S, surgery.

other hand, some recommendations from the guidelines were not implemented in actual practice. Although EN was strongly recommended in the guidelines, it was not commonly used, even in patients with severe AP. Although the guidelines do not recommend the administration of prophylactic antibiotics to patients with mild AP, 73.0% of patients with mild AP received antibiotics. In agreement with our study, an international multicenter survey by Talukdar et al[20] reported poor compliance with the guidelines for the early management of AP; only 41.9% of patients were treated in compliance with feeding guidelines, and 59.7% of patients were treated in compliance with antibiotic guidelines. Proper compliance with these guidelines would further improve the management of patients with AP.

If stratified by age groups, males had higher mortality than females in almost all age groups, except for those aged 40 to 49 years. This finding agree with that of a recent study from the United States showing that female patients with AP had better clinical outcomes, including a lower risk of mortality, shock, sepsis, acute kidney injury, ICU admission, and pancreatic drainage than male patients with AP.[21] Genetic, environmental, and hormonal differences might play a role in the sex differences in outcomes of AP patients as in the case of liver diseases.[22] The predominant etiology of biliary AP in women and alcohol-related AP in men might be one explanation; however, the mortality in patients with alcohol-related AP (1.2%) was lower than that in patients with biliary AP (1.7%) in a recent Japanese nationwide survey.[6] Further elucidation of the underlying mechanisms would contribute to both triage planning and tailor treatment because the current management of AP is the same for both men and women. Meanwhile, we observed that mortality increased with age. This was not surprising because previous studies have shown the association between mortality and advanced age in patients with AP, and age 70 years or older has been included in the Japanese severity criteria.[15] Recently, Kayar et al[23] reported that the mortality in patients with AP older than 65 years was higher than that in patients younger than 65 years (3.5% vs 0.5%). Evidently, mortality is higher in the elderly because of their reduced organ function. As the Japanese population is aging, it is likely that patients with AP will be older in the future, and the presence of comorbidities might further increase the mortality in elderly patients.[24]

The Japanese severity criteria consist of 9 prognostic factors and CT grading.[16] Contrast-enhanced CT is an essential method for the assessment of CT grading, and it is commonly performed for the management of AP in Japan. It was performed in 90.8% of patients with AP and in 95% of patients with severe AP.[19] In this study, the mortality in patients with severe AP who were diagnosed based on the prognostic factor score was only higher than that in patients who were diagnosed based on CT grading only (11.1% vs 2.3%, $P < 0.001$). Previous studies have shown the utility of the prognostic factor score for predicting outcomes in patients with AP.[13,25,26] At 48 hours after admission, the prognostic factor score was the best among the commonly used scoring systems such as the Ranson score and Acute Physiology and Chronic Health Evaluation II score for predicting persistent organ failure.[25] A systematic review showed that the prognostic factor score and the Bedside Index of Severity in Acute Pancreatitis were the best predictors of persistent organ failure if evaluated within 48 hours of admission, whereas the prognostic factor score and blood urea nitrogen levels were the best predictors after 48 hours of admission.[26] One explanation for the low mortality in patients who were diagnosed based on CT grading only might be the overestimation of severity. Majority of these patients were classified as patients with severe AP merely due to the progression of inflammation beyond the lower pole of the kidney, resulting in the absence or limited presence of hypoenhanced area in the pancreas.[6] If 15,263 patients who were diagnosed based on CT grading only were classified as patients with mild AP, patients with severe AP would account for 8.4% (6707/79,455) of the patients in whom the severity of AP was determined, and the mortality in patients with severe AP would be 13.4% (896/6707). Importantly, patients who were diagnosed with severe AP based on both prognostic factors and CT grading had a mortality of 15.0% in this study and 19.8% in the latest nationwide survey.[6] Cases that were diagnosed with severe AP based on both prognostic factors and CT grading should be regarded as the most severe cases and should be managed with caution. In daily practice, the severity of AP should be repeatedly assessed using the prognostic factor score, which includes physiologic and laboratory data, and contrast-enhanced CT should be performed only if the patient was classified as a patient with severe AP according to the prognostic score.

In contrast to the early mortality, the late mortality remained unchanged. Infected pancreatic necrosis is a major determinant of mortality in patients with AP in the late phase of hospitalization,[26] and the mortality in patients who required intervention for local complications was 12.2%. Minimally invasive endoscopic approaches such as EUS-guided transluminal drainage with the placement of a plastic or a lumen-apposing metal stent and endoscopic necrosectomy, which were included as EUS-guided fistuloplasty in this study, have become increasingly popular.[27,28] The proportion of patients who underwent EUS-guided fistuloplasty as an initial intervention increased from 45.1% in the first period to 55.6% in the second period. The mortality in patients who underwent EUS-guided treatment was lower than that in patients who underwent percutaneous drainage or surgery. In addition, mortality increased if patients underwent procedures, such as percutaneous drainage and surgery, in addition to endoscopic treatment. These results suggest the superiority of endoscopic intervention over surgery for the management of local complications and the intractable nature of the disease in patients who require additional procedures to control local complications. Unlike some randomized controlled trials,[29] a meta-analysis of randomized controlled trials showed the superiority of endoscopic intervention over surgery.[30] Standardization and technical improvements of the management of local complications are essential for reducing mortality in the late phase of hospitalization.

This study has some limitations, including those due to the nature of the DPC database. First, the database relies on the accuracy of *ICD-10* code for AP, and it is limited to inpatient settings and retrospective in nature. Second, information including the etiology and laboratory data was unavailable. Third, except for CT grading, imaging findings were not available. Fourth, we could not distinguish between AP-related deaths and deaths unrelated to AP. Lastly, we could not identify some procedures because specific codes were absent. Despite these limitations, we could clarify the clinical practice of AP. This study also revealed the improvement in prognosis after revision of the Japanese guidelines. Further compliance with the guidelines would contribute to improved prognosis of this intractable disease.

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